Mechanisms in the Transmission of Intergenerational Trauma: The Role of Placental Corticotrophin-Releasing Hormone in Transmitting the Experiences of Maternal Childhood Trauma

Abstract

Intergenerational trauma is a theory that trauma in one generation can be passed down through generations of offspring. This paper investigates the mechanisms of this transmission by looking at the role of the production of placental corticotrophin-releasing hormone (pCRH) in mothers who had experienced childhood trauma and those that did not, across gestational age. CRH is primarily responsible for controlling the stress network in the body and is also synthesized in the placenta during pregnancy. Since placental CRH is secreted in both the fetal and maternal circulations [3] it is hypothesized as a primary driver of this transmission. To carry out this investigation, three methods were performed controlling for appropriate confounding variables: a frequentist linear mixed effects model, Bayesian hierarchical model, and a Bayesian hierarchical model with a spline at approximately twenty weeks into gestation. The three models agree that mothers who experienced childhood trauma begin gestation with lower levels of pCRH, but have a rate of production that is greater than those who did not experience childhood trauma, eventually ending pregnancy with higher levels of pCRH (all other factors held constant).

1 Introduction

Intergenerational trauma is associated with the theory that trauma in one generation can be passed down through generations of offspring, affecting behavioral and psychiatric outcomes and prognoses. What is unclear though is by which biological or environmental mechanisms this transmission occurs. This paper explores the hypothesis that this intergenerational transmission begins in the womb through the effect of maternal childhood trauma exposure on placental-fetal stress physiology, specifically the production of placental corticotrophin-releasing hormone (pCRH).

The hypothesis of an intergenerational transmission of psychoses has been considered since the 1800's, but the concept was not truly explored until analyses of Holocaust survivors and their offspring in the 1960's [5]. Studies have shown that offspring of Holocaust survivors and other trauma survivors, after experiencing their own traumas, were more vulnerable to post-traumatic stress disorder (PTSD), and often times had 'a different clinical picture' when compared with patients whose parents did not experience trauma [6]. Yehuda et al. (2001) performed a study comparing Holocaust survivors and concluded that the experience of childhood trauma specifically, was an important factor in the transmission of these psychiatric disorders from parent to child[7].

We further explore this hypothesis by considering the relationship of maternal childhood trauma exposure on placental-fetal stress physiology and the production of pCRH. Corticotrophin-Releasing Hormone (CRH) is

the primary controller of the hypothalamic-pituitary-adrenal axis, which is also known as the stress hormone system. CRH causes the release of adrenocorticotropic hormone from the pituitary gland, which in turn causes the secretion of cortisol. Therefore higher levels of CRH within the body correspond to episodes of higher stress, primarily as a response mechanism to mobilize resources in the body [1].

Placental corticotrophin-releasing hormone is CRH that is made in the placenta during pregnancy, and is secreted in both the fetal and maternal circulations [3]. The expression of pCRH increases exponentially throughout pregnancy and increases as much as 100 times during the last 6 to 8 weeks of pregnancy [3]. As pCRH is responsible for human response to stress, and is secreted in both the maternal and fetal circulations, it is interesting to investigate the role of maternal childhood trauma on the production of pCRH and in turn the corresponding fetal exposure to pCRH.

In order to address the relationship between pCRH and maternal childhood trauma, three methods will be outlined and compared. Specifically a frequentist linear mixed effects model will be developed and compared against a Bayesian hierarchical model, in order to capture individual level differences in baseline pCRH within the cohort. For both models, appropriate confounding variables will be included and controlled for that potentially correspond to the levels of pCRH development. Finally, it is also hypothesized that around week 20 of pregnancy the rate of change in pCRH production changes drastically. A Bayesian hierarchical model with a spline at approximately week 20 will be utilized to address this secondary hypothesis.

1.1 Dataset Description

Data for this analysis come from a socio-demographically diverse cohort of 88 pregnant women. Placental CRH concentrations were quantified in maternal blood collected longitudinally through gestation between weeks 14 and 40; observed were three to five measurements per mother. Childhood trauma (CT) exposure was assessed using the Childhood Trauma Questionnaire. The questionnaire is a 28-item measure that assesses five dimensions of childhood maltreatment: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. CT exposure was delivered as the cumulative total number of exposures that were experienced throughout childhood.

Also included with the dataset are measurements for confounding variables including depression, obstetric risk indicators, maternal body mass index, socioeconomic scores, and parity. Depression was measured based upon a questionnaire created by the Center for Epidemiological Studies (CESD). Socioeconomic status was quantified using a 15-item measure that characterizes distinct aspects of economic status during childhood.

1.2 Analysis Goals and Objectives

1. Examine the effect of childhood trauma (CT) exposure on pCRH production over gestational age using **frequentist methods** while controlling for potential confounding factors
2. Examine the effect of childhood trauma (CT) exposure on pCRH production over gestational age using **Bayesian methods** while controlling for potential confounding factors
3. Investigate the rate of change in pCRH production before and after approximately week 20 into pregnancy. Develop a model to address this change in the rate of pCRH comparing trauma survivors and those who did not experience trauma

2 Statistical Methods

2.1 Preliminary Data Exploration

Prior to addressing the scientific goals and objectives outlined in Section 1, it was necessary to explore the dataset to identify interesting features within the data. First a transformation was performed of the

Figure 1: Graphics 1 & 2: Temporal trend of the logarithmic transformation of placental corticotrophin-releasing hormone *log(pCRH)* compared against those who experienced trauma and those that did not. Note: Jitter was added to Gestational Age for clearer visual presentation. See Appendix A for a graphical depiction of the variable on the original scale. Graphic 3: Binned Gestational Age by five weeks to compare differences in log(pCRH) between trauma exposure and no trauma exposure.

variable representing the cumulative sum of childhood traumas into a binary indicator to identify those who had experienced childhood trauma and those who did not. This allows us to answer the question as to whether exposure to childhood trauma effects pCRH production and to not concern ourselves with the levels of childhood trauma. The second transformation was a logarithmic transformation of the response pCRH. Majzoub et al. (1998) suggested that levels of pCRH increase as much as 100 times during the last 6 to 8 weeks of pregnancy, thus it was believed that a logarithmic transformation would be appropriate for the response. Appendix A highlights the difference between the non-transformed and transformed response.

To summarize the temporal trend in pCRH production across gestation, Figure 1 was generated to compare the trends between mothers who had experienced trauma and those that did not and to highlight individual trajectories. The difference between these two treatments is not completely obvious in the first two graphics of Figure 1, but noticeable is the hypothesized change in the rate of production at approximately week 20 as evident by an 'elbow' in the plots. Though jitter was added to the plots, notice that measurements for pCRH were taken around 5 specific clusters of weeks during pregnancy.

The third graphic in Figure 1 bins the observations by these five different 'clusters' of observations and better identifies the differences in pCRH production throughout gestation. Clearly the median log(pCRH) level is higher for weeks 14-35 for those mothers who did not experience trauma, though we see less of a difference between the two groups at the end of pregnancy, suggesting an interaction between gestational age and childhood trauma. Finally appealing to Figure 2 not every mother had pCRH measured in each of these five intervals, this will be addressed in the modeling phase of the analysis.

	Experienced Trauma		*Did Not Experience Trauma*	
	Mean (Counts)	Std. Dev. (Percent)	Mean (Counts)	Std. Dev. (Percent)
Total Number of Childhood Traumas	2.093	0.996	0	-
Depression Score	0.844	0.458	0.46	0.326
Childhood Socioeconomic Score	11.163	3.062	11.822	2.443
Parity (# of Previous Pregnancies)	1	1.091	0.867	0.919
# of Mothers with Obstetric Risk Conditions	17	39.5%	11	24.4%
Total Counts	43	48.9%	45	51.1%

Table 1: Summary statistics for variables that were only measured once during gestational age (do not vary across GA). Notice that the two groups are similar across many variables including Childhood Socioeconomic Score and Parity. Worth noting is the difference between CES-D Depression scores between those who had experienced childhood trauma and those that did not.

Table 1 summarizes the variables that do not vary with time within the dataset. There are a total of 43

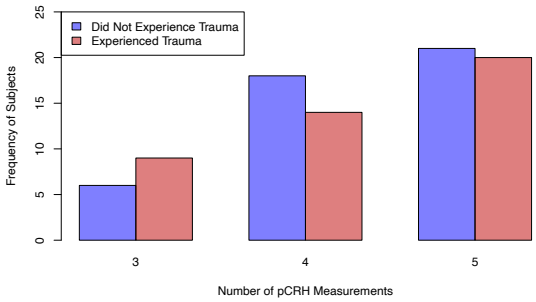

Figure 2: Distribution of the number of observations per mother. There is an unbalanced number of observations across mothers, but the distribution of each number of observations is similar between trauma types.

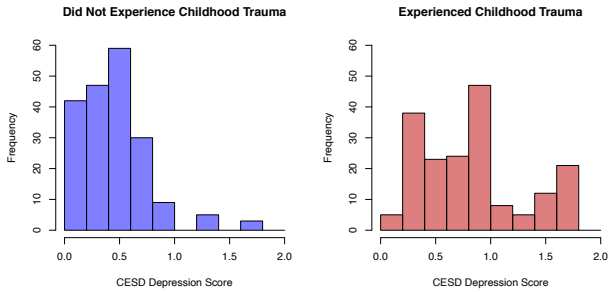

Figure 3: Distribution of depression scores comparing those who experienced trauma and those that did not. There is an underrepresentation of mothers with a higher depression score who did not experience trauma.

mothers who experienced childhood trauma and a total of 45 mothers that did not. The two different groups of mothers are similar across many of the different variables included, differing primarily in their designation of childhood trauma. It is advantageous that mothers are similar across childhood socioeconomic status and risk status to ensure valid inference between the two groups.

Finally the only notable difference between the two groups is that mothers who experienced trauma had a higher mean depression score compared with those that did not. The distribution of the depression scores is shown in Figure 3 and illustrates that the depression profiles between the two groups differ slightly. This result could be expected due to the traumatic experiences throughout their lives.

2.2 Modeling Process and Methodology

2.2.1 Linear Mixed Effects Model

In order to handle the longitudinal nature of the response variable, as well as the unbalanced number of observations demonstrated in Figure 2, we utilize a linear mixed effects model similar to those presented in Laird and Ware (1982). This 'two-stage' model has the desirable advantage that it does not require balance within the data [2], thus there is no need to impute missing observations to balance the number of observations per mother. This class of models also gracefully handles the longitudinal nature of our response, log(pCRH).

Now letting i represent the i^{th} individual within the study and let j represent the j^{th} measurement for that individual, consider the following model:

$$log(pCRH)_{i,j} = (\alpha_{0,i} + \beta_0) + \beta_1 CT_i + \beta_2 GA_{i,j} + \beta_3 CT_i \times GA_{i,j} + \phi_i(\text{confounding variables}) + \epsilon_{i,j} \quad (1)$$

$$\epsilon_{i,j} \sim_{i.i.d.} N(0, \sigma^2_\epsilon)$$
$$\alpha_{0,i} \sim_{i.i.d.} N(0, \sigma^2_\alpha)$$

where $\phi(\cdot)$ is a linear function of the confounding variables: CESD, CSES, BMI, OBRisk, and Parity, with appropriate β_k coefficients. Explicitly, that is,

$$\phi_i(\text{confounding variables}) = \beta_4 CESD_i + \beta_5 CSES_i + \beta_6 BMI_i + \beta_7 OBRisk_i + \beta_8 Parity_i \tag{2}$$

Note: This function of the confounding variables will be used throughout the modeling section.

The above model includes our primary covariate's of interest CT and GA as well as an interaction that was suggested by the non-constant difference in the treatment groups comparing log(pCRH) across gestational age in Figure 1. The model includes all confounding variables in the model since they all could reasonably be associated with stress, for which CRH plays a critical role and should therefore be controlled.

Also included in the model are individual intercept terms, $\alpha_{0,i}$. These represent the random effects and allow variation in individual levels of log(pCRH) at baseline. It was decided to not include random effects for the slope terms based upon preliminary data exploration. Figure 1 shows that individuals do not have wildly varying slopes and those that begin with lower log(pCRH) tend to end with lower log(pCRH) (similarly for the reverse), thus the author believes only a random effect for the intercept is adequate for this analysis.

To fit this model we will use the *nlme* package in the R programming language that was developed specifically using the methods of Laird and Ware (1982) [4].

2.2.2 Bayesian Hierarchical Model

Considering (1), if we define Y_i to be the vector representing all J_i values of $log(pCRH)_{i,j}$ for the i^{th} individual, define α to be a vector containing each of the n individual random effects, define β to be the vector of the k parameters, and construct X_i and Z_i appropriately, (1) can be written in the following manner:

$$Y_i = Z_i\alpha + X_i\beta + \begin{pmatrix} \epsilon_{i,1} \\ \epsilon_{i,2} \\ \vdots \\ \epsilon_{i,J_i} \end{pmatrix} \text{ for } i = 1, \ldots, n$$

Here again, $\epsilon_{i,j} \sim_{i.i.d.} N(0, \sigma^2_\epsilon)$, which captures the systematic variability in the measurements.

From this model definition we can construct the following hierarchical Bayesian model for our analysis,

$$\begin{aligned}
Y|\alpha, \beta, Z, X, \sigma^2_\epsilon &\sim N_N(X\beta + Z\alpha, \sigma^2_\epsilon I_{N\times N}) \\
\alpha_i|\sigma^2_\alpha &\overset{iid}{\sim} N(0, \sigma^2_\alpha) \\
\beta|\sigma^2_\beta &\sim N_k(0, \sigma^2_\beta I_{k\times k}) \\
\sigma^2_\epsilon|\nu_0, \sigma^2_0 &\sim \text{Inv-}\chi^2(\nu_0, \sigma^2_0) \\
\sigma^2_\alpha|\nu_1, \sigma^2_1 &\sim \text{Inv-}\chi^2(\nu_1, \sigma^2_1)
\end{aligned}$$

where $n \equiv$ total number of individuals, $N \equiv$ total number of observations.

The above model is developed so that each individual specific component comes from a population of parameters centered at zero with some variance σ^2_α, that is, we are assuming a priori that there is no individual specific component in addition to baseline log(pCRH) measurements. We have placed a conjugate prior on σ^2_α that is distributed inverse chi-square with hyperparameters (ν_1, σ^2_1), For the β parameters and σ^2_ϵ we use conjugate priors for the normal distribution with appropriate hyperparameters to simplify posterior sampling with Gibbs sampling.

In order to sample from the posterior distributions, we will utilize a Gibbs sampling algorithm outlined in Appendix C without the optional Metropolis-Hastings step. The following hyperparameters were selected:

$$\begin{aligned} \beta|\sigma_\beta^2 &\sim N_9(0, 10 \times I_{9\times 9}) \\ \sigma_\epsilon^2|\nu_0, \sigma_0^2 &\sim \text{Inv-}\chi^2(1, 0.5) \\ \sigma_\alpha^2|\nu_1, \sigma_1^2 &\sim \text{Inv-}\chi^2(1, 0.5) \end{aligned}$$

The hyperparameters for β were selected to provide mild regularization to the posterior estimates and reflect a lack of expert knowledge for relationships between each β_k and the response log(pCRCH). The hyperparameters for σ_α^2 and σ_ϵ^2 were selected similarly.

2.2.3 Bayesian Piecewise Regression

Finally to address the hypothesis of a change in the rate of pCRH production at approximately week 20, we modify the model in section 2.2.2. First augment (1) to include a spline at a location τ at some point along gestation. That is

$$\begin{aligned} log(pCRH)_{i,j} &= (\alpha_{0,i} + \beta_0) + \beta_1 CT_i + \beta_2 GA_{i,j} + \beta_3 CT_i \times GA_{i,j} \\ &\quad + \beta_9 (GA_{i,j} - \tau)_+ + \beta_{10} CT_i \times (GA_{i,j} - \tau)_+ \\ &\quad + \phi_i(\text{confounding variables}) + \epsilon_{i,j} \end{aligned}$$

where $(GA_{i,j} - \tau)_+$ subtracts the value for the spline at each point $GA_{i,j}$ and if this value is negative, it is set to zero.

We can then augment the hierarchical model in section 2.2.2 as follows where X is now a function of τ:

$$\begin{aligned} Y|\alpha, \beta, Z, X, \sigma_\epsilon^2, \tau &\sim N_N(X(\tau)\beta + Z\alpha, \sigma_\epsilon^2 I_{N\times N}) \\ \alpha_i|\sigma_\alpha^2 &\overset{iid}{\sim} N(0, \sigma_\alpha^2) \\ \beta|\sigma_\beta^2 &\sim N_k(0, \sigma_\beta^2 I_{k\times k}) \\ \sigma_\epsilon^2|\nu_0, \sigma_0^2 &\sim \text{Inv-}\chi^2(\nu_0, \sigma_0^2) \\ \sigma_\alpha^2|\nu_1, \sigma_1^2 &\sim \text{Inv-}\chi^2(\nu_1, \sigma_1^2) \\ \tau|\mu_\tau, \sigma_\tau^2 &\sim N(\mu_\tau, \sigma_\tau^2) \end{aligned}$$

We assume a prior $\tau|\mu_\tau, \sigma_\tau^2 \sim N(20, 0.1)$, which places 95% of the prior probability on values of τ between (19.3802, 20.6198) reflecting the prior knowledge that the change in the rate of production occurs around week 20.

The posterior for $p(\tau|\vec{\theta}_{-\tau})$ was not of an easily recognizable distribution for a simple incorporation into the Gibbs sampling algorithm, so a Metropolis-Hastings step was added as the final stage of the algorithm to sample for the posterior of τ. The proposal distribution for $\tau^*|\tau^{(t)}$ was selected as truncated normal distribution, centered at the previous $\tau^{(t)}$, with variance $\delta = 1$ and truncation points $(l = 0, r = \infty)$ to ensure non-negative proposals for τ^*.

Please refer to Appendix C for the full algorithm that was used for posterior sampling.

3 Results

In order to address analysis goals one and two, a frequentist linear mixed effects model and a Bayesian hierarchical model were fit with coefficient estimates and posterior estimates located in Table 2. Estimates are presented side by side to highlight the similarity between the two models and show that they provide almost equivalent results.

	Frequentist Linear Mixed Effects Model					*Bayesian Heirarchical Model*			
Parameter	Coef. Est.	S.E.	2.5%	97.5%	P-Value	Post. Med.	S.E.	2.5%	97.5%
$(Intercept)$	1.8645	0.2813	1.3110	2.4181	0.0000	1.8503	0.2952	1.2614	2.4309
$(CT = 1)$	-0.4413	0.1871	-0.8136	-0.0690	0.0208	-0.4391	0.1974	-0.8247	-0.0543
GA	0.1387	0.0041	0.1307	0.1467	0.0000	0.1388	0.0044	0.1302	0.1473
$(CT = 1) \times GA$	0.0162	0.0059	0.0045	0.0279	0.0069	0.0160	0.0063	0.0036	0.0286
Confounding Var.	*For Confounding Variables See Appendix B*								
σ_ϵ	0.4144	-	0.3819	0.4498	-	0.4436	0.0242	0.4031	0.4977
σ_α	0.3418	-	0.2767	0.4222	-	0.3463	0.0369	0.2813	0.4254

Table 2: Coefficient Estimates and intervals from the frequentist linear mixed model compared against the posterior estimates from the Bayesian hierarchical model. Coefficient estimates for confounding variables can be found in the Appendix.

The primary result from this table is that within the frequentist linear mixed effects model the variables of maternal childhood trauma, gestational age and the interaction between maternal childhood trauma and gestational age, are significantly associated with pCRH production. The Bayesian hierarchical model suggests a similar result with all of the posterior 95% credible intervals outside zero. These findings further suggest that there is a significant relationship between exposure to childhood trauma and levels of pCRH across gestational age.

Specifically, we see that at approximately week 14 of gestational age, the contribution to mean log(pCRH) based upon childhood trauma, when comparing two groups of mothers, one who experienced trauma against one that did not (all other factors constant), was approximately -0.2145 units, while at week 40 that contribution reverses to +0.2067 units. This can be more simply stated that mothers who experienced trauma begin pregnancy with lower levels of pCRH, but by the end of pregnancy exhibit higher levels of pCRH when comparing against mothers who were not exposed to trauma, all other factors held constant. This result is highlighted in Figure 4, where the posterior estimates for the differences in the curves from the Bayesian hierarchical model with posterior credible intervals are shown. Both models fit the data adequately for larger fitted values based on residual plots in Appendix D, but we see that the model may be slightly misspecified by the shape of the residuals for lower fitted values.

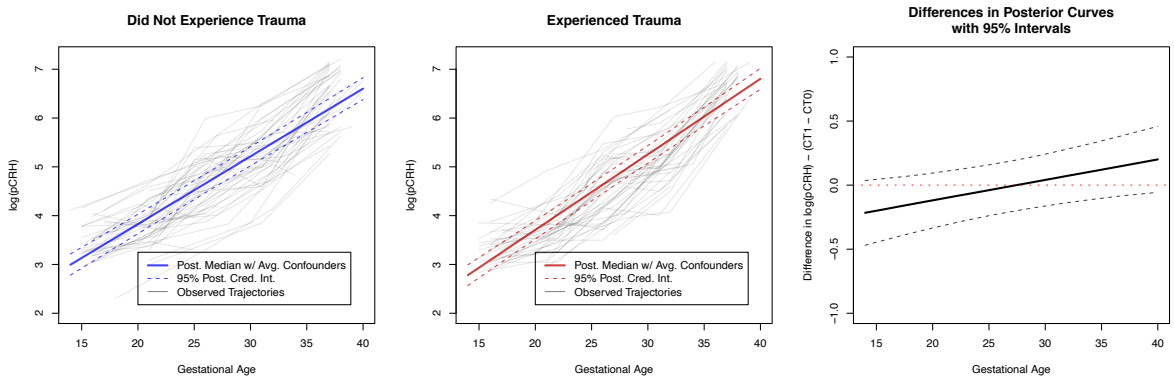

Figure 4: Comparing the trends from the mean trends from the Bayesian hierarhical model. Values for confounding variables for each group were the mean values across the dataset for continuous variables and $OBRisk$ set to 1.

To address the change in the rate of production at approximately week 20 and correct the model fit for lower fitted values, the Bayesian hierarchical model was adjusted and a spline was introduced into the model. Figure 5 and Table 3 show that the posterior median for the location of the spline, τ, was approximately 19.8 (16.9-21.8, 95% credible interval). The figure identifies some variability in its location, but some of this variability may be attributed to a sparseness of sampling at these times points (Figure 1).

Posterior estimates from the Bayesian hierarchical model with the spline are located in Table 3. The results from this analysis are similar with the previous two and by visual inspection of Figure 6, appear to have a

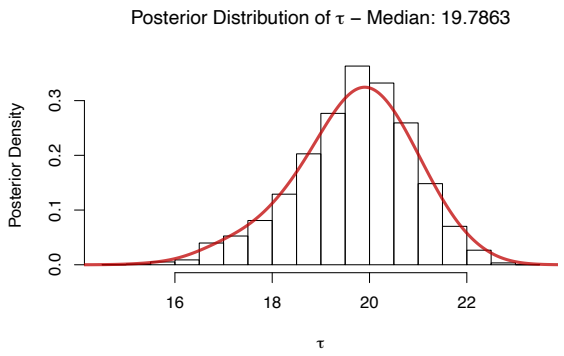

Figure 5: Posterior distribution of τ. The location of the change in the production is at approximately 20 weeks.

	Bayesian Heirarchical Model with Spline			
Paramter	Post. Med.	S.E.	2.5%	97.5%
$(Intercept)$	3.4308	0.8338	2.2845	5.6010
$(CT = 1)$	0.6598	0.9667	-0.7369	3.1801
GA	0.0516	0.0484	-0.0849	0.1046
$(CT = 1) \times GA$	-0.0449	0.0565	-0.1979	0.0301
$(GA - \tau)_+$	0.1017	0.0495	0.0411	0.2371
$(CT = 1) \times (GA - \tau)_+$	0.0716	0.0598	-0.0151	0.2265
	For Confounding Variables See Appendix B			
σ_ϵ	0.4422	0.0773	0.3816	0.6711
σ_α	0.3512	0.0443	0.2818	0.4526
τ	19.7863	1.2040	16.9330	21.7958

Table 3: Bayesian hierarchical modeling with spline. Coefficient estimates for confounding variables can be found in the Appendix.

better model fit. Supporting this inspection, residual plots in Appendix D show the misspecification of the model for low fitted values has been corrected.

A major result from the table is that prior to the knot, mothers who were not exposed to trauma have a slightly higher rate of production of pCRH, but at approximately week 20 the production of pCRH increases in exposed mothers and eventually overtakes the early gains by non-exposed mothers. These results also suggest that at gestational week 40 the contribution to the mean log(pCRH) based upon exposure to childhood trauma would be approximately +0.3102 units higher (all other factors constant) when comparing against mothers who were not exposed. This is notable because by adjusting the model for the spline location the final contribution to the mean log(pCRH) response was able to increase and there is a more pronounced difference between the two groups at the end of gestation. Figure 6 highlights the difference in the mean log(pCRH) response between mothers who experienced trauma and those that did not across gestation with 95% credible intervals. We see that there is still a marginally significant difference between the two models at the end of gestation after the addition of the spline location into the model.

The three models generally agree that mothers who experienced childhood trauma begin gestation with lower levels of log(pCRH), but have a higher rate of production across gestation than those who did not experience childhood trauma, eventually ending pregnancy with higher levels of log(pCRH) (all other factors held constant).

Figure 6: Comparing the mean trends from the Bayesian hierarchical model with splines. Values for confounding variables for each group were the mean values across mothers.

4 Conclusion

4.1 Limitations

The results from this analysis were adequate to answer the fundamental question of the relationship between maternal childhood trauma and the production of pCRH across gestational age, but could have been made more robust. Since this is an observational study, we are subject to the non-randomization of the treatment assignment and are limited in the conclusions that we can make. Clearly there are both ethical and moral reasons that we cannot randomize the treatment of maternal childhood trauma, but future studies could be supplemented by propensity score methods or other causal statistical techniques to balance the covariates of those who were exposed to childhood trauma and those that were not and make stronger claims.

Additionally, the study could have been benefited from more covariates measured throughout the study. Primarily, the age of the mother throughout gestation and the sex of the child are two factors that were not provided in this analysis, but may have been beneficial to control for. The age of the mother could impact the body's response to stress, or biologically the production of pCRH, and should be considered as a confounding variable within the study. The gender of the child could also play a role in the biological response of the mother and would have been an interesting confounding variable to control for. Overall though, the study was able to address the primary question of interest and further studies that investigate this relationship should consider the factors mentioned.

4.2 Discussion

The primary goal of this analysis was to investigate the hypothesis that childhood trauma in one generation could be passed along to the next via some biological mechanism. Investigated specifically was the role placental corticotrophin-releasing hormone and levels of this hormone across gestation. To carry out this investigation, three methods were performed: a frequentist linear mixed effects model, Bayesian hierarchical model, and a Bayesian hierarchical model with a spline at approximately twenty weeks into gestation.

The frequentist linear mixed effects model was fit using the R package *nlme*, while the Bayesian hierarchical model was fit using a Gibbs sampling algorithm in Appendix C. These two models were constructed such that the Bayesian model replicated the findings from the linear mixed effects model, but under the Bayesian paradigm. Both models controlled for the confounding variables that were included in the dataset. The final model was another Bayesian hierarchical model, with the addition of a spline, that was fit using the Gibbs sampler in Appendix C. The model allowed for the posterior sampling of the spline location, τ as well as the other parameters. The addition of this spline to the model was able to correct a misspecification of the model for smaller fitted values.

The analysis was able to find a difference between the production of pCRH across gestation in mothers who experienced childhood trauma against those who did not, while controlling for a variety of factors. The basic finding is that generally mothers who had been exposed to childhood trauma began pregnancy with lower levels of pCRH, but had a higher rate of production across gestational age (Figures 4 & 6), ultimately ending pregnancy with elevated levels of pCRH as compared with mothers who did not experience childhood trauma (other factors constant). This result could have major practical significance if indeed pCRH is instrumental in the development of the childhood stress response system and could hopefully in the future identify ways to mitigate the transmission of intergenerational trauma.

The analysis that was performed was able to address the scientific questions of Section 1.2 and provided interesting insights into the relationship between maternal childhood trauma exposure and the production of pCRH across gestational age.

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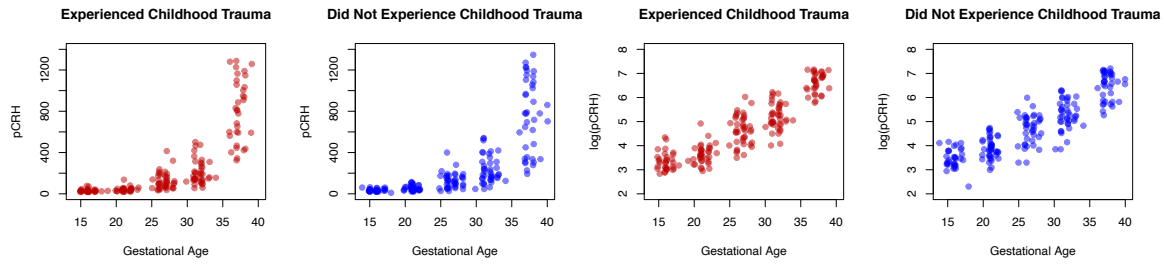
Appendix

A Transformation of the Response



B Complete Parameter Estimates

	Frequentist Linear Mixed Effects Model					*Bayesian Heirarchical Model*			
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GA	0.1387	0.0041	0.1307	0.1467	0.0000	0.1388	0.0044	0.1302	0.1473
$(CT = 1) \times GA$	0.0162	0.0059	0.0045	0.0279	0.0069	0.0160	0.0063	0.0036	0.0286
$CESD$	-0.0505	0.1106	-0.2705	0.1695	0.6490	-0.0502	0.1134	-0.2681	0.1786
$CSES$	-0.0209	0.0156	-0.0520	0.0102	0.1841	-0.0206	0.0161	-0.0522	0.0114
BMI	-0.0212	0.0073	-0.0357	-0.0068	0.0045	-0.0208	0.0076	-0.0356	-0.0061
$OBRisk$	0.0518	0.0933	-0.1338	0.2375	0.5800	0.0517	0.0952	-0.1344	0.2379
$Parity$	-0.0750	0.0435	-0.1615	0.0116	0.0887	-0.0753	0.0450	-0.1633	0.0132
σ_ϵ	0.4144	-	0.3819	0.4498	-	0.4436	0.0242	0.4031	0.4977
σ_α	0.3418	-	0.2767	0.4222	-	0.3463	0.0369	0.2813	0.4254

	Bayesian Heirarchical Model with Spline			
Paramter	Post. Med.	S.E.	2.5%	97.5%
$(Intercept)$	3.4308	0.8338	2.2845	5.6010
$(CT = 1)$	0.6598	0.9667	-0.7369	3.1801
GA	0.0516	0.0484	-0.0849	0.1046
$(CT = 1) \times GA$	-0.0449	0.0565	-0.1979	0.0301
$(GA - \tau)_+$	0.1017	0.0495	0.0411	0.2371
$(CT = 1) \times (GA - \tau)_+$	0.0716	0.0598	-0.0151	0.2265
$CESD$	-0.0495	0.1173	-0.2768	0.1828
$CSES$	-0.0215	0.0166	-0.0542	0.0110
BMI	-0.0200	0.0077	-0.0353	-0.0050
$OBRisk$	0.0564	0.0981	-0.1348	0.2510
$Parity$	-0.0786	0.0463	-0.1687	0.0125
σ_ϵ	0.4422	0.0773	0.3816	0.6711
σ_α	0.3512	0.0443	0.2818	0.4526
τ	19.7863	1.2040	16.9330	21.7958

C General Gibbs Sampling Algorithm (with Optional Metropolis Step)

Define where $n \equiv$ total number of individuals, $N \equiv$ total number of observations. and $k \equiv$ the total number of parameters.

Define $\Sigma_\beta^{(t)} = \frac{1}{\sigma_\epsilon^{2(t)}} X^T X + \frac{1}{\sigma_\beta^2} I_{k\times k}$, and $\Sigma_\alpha^{(t)} = \frac{1}{\sigma_\epsilon^{2(t)}} Z^T Z + \frac{1}{\sigma_\alpha^{2(t)}} I_{n\times n}$

General Gibbs Sampling Algorithm (with Optional Metropolis-Hastings Step)

- Initialize $\beta^{(0)}$ (via OLS), $\alpha^{(0)}$, $\sigma_\alpha^{2(0)}, \sigma_\epsilon^{2(0)}, \sigma_\beta^2, \nu_0, \sigma_0$
- Until Convergence, Sample

$$\begin{aligned}
\beta^{(t+1)}|Y,Z,X,\alpha^{(t)},\sigma_\epsilon^{2(t)},\sigma_\alpha^{2(t)} &\sim N\Big(\big(\Sigma_\beta^{(t)}\big)^{-1}\big(\frac{1}{\sigma_\epsilon^{2(t)}} X^T(Y - Z\alpha^{(t)})\big), \big(\Sigma_\beta^{(t)}\big)^{-1}\Big) \\
\alpha^{(t+1)}|Y,Z,X,\beta^{(t+1)},\sigma_\epsilon^{2(t)},\sigma_\alpha^{2(t)} &\sim N\Big(\big(\Sigma_\alpha^{(t)}\big)^{-1}\big(\frac{1}{\sigma_\epsilon^{2(t)}} Z^T(Y - X\beta^{(t+1)})\big), \big(\Sigma_\alpha^{(t)}\big)^{-1}\Big) \\
\sigma_\epsilon^{2(t+1)}|Y,Z,X,\beta^{(t+1)},\alpha^{(t+1)},\sigma_\alpha^{2(t)} &\sim \text{Inv-}\chi^2\Big(\nu_0 + N, \frac{\nu_0\sigma_0^2 + K^*}{\nu_0 + N}\Big) \\
&\quad \text{where } K^* \equiv (Y - (X\beta^{(t+1)} + Z\alpha^{(t+1)}))^T(Y - (X\beta^{(t+1)} + Z\alpha^{(t+1)})) \\
\sigma_\alpha^{2(t+1)}|Y,Z,X,\beta^{(t+1)},\alpha^{(t+1)},\sigma_\epsilon^{2(t)} &\sim \text{Inv-}\chi^2\Big(\nu_1 + n, \frac{\nu_1\sigma_1^2 + (\alpha^{(t+1)})^T\alpha^{(t+1)}}{\nu_1 + n}\Big)
\end{aligned}$$

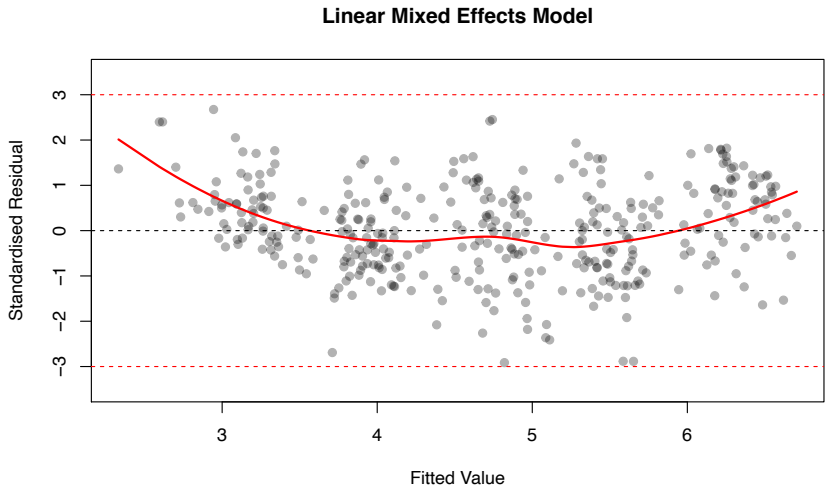
  - (Optional) - Sample knot location τ if included in X.
    - Define:

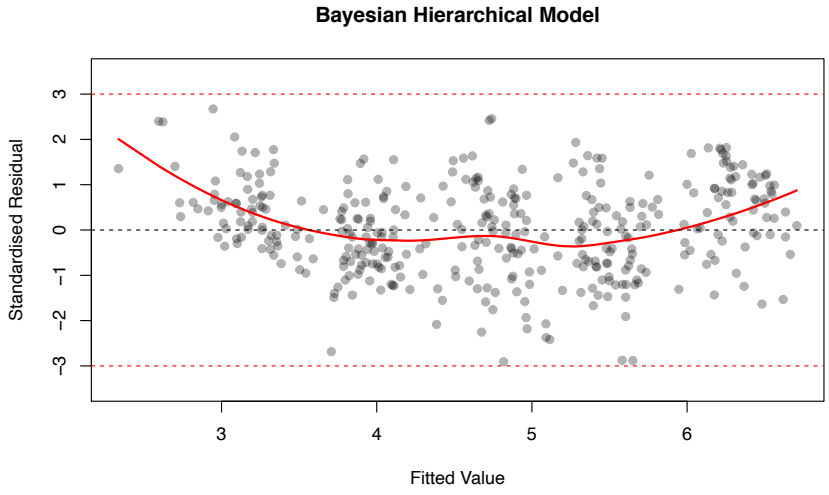
$$\begin{aligned}
p(\tau|Y,Z,X,\beta^{(t+1)},\alpha^{(t+1)},\sigma_\epsilon^{2(t)},\sigma_\alpha^{2(t+1)}) &\propto \exp\Big(-\frac{K^\tau}{2\sigma_\epsilon^2} - \frac{(\tau-\mu_\tau)^2}{2\sigma_\tau^2}\Big) \\
&= p(\tau|\cdot)
\end{aligned}$$

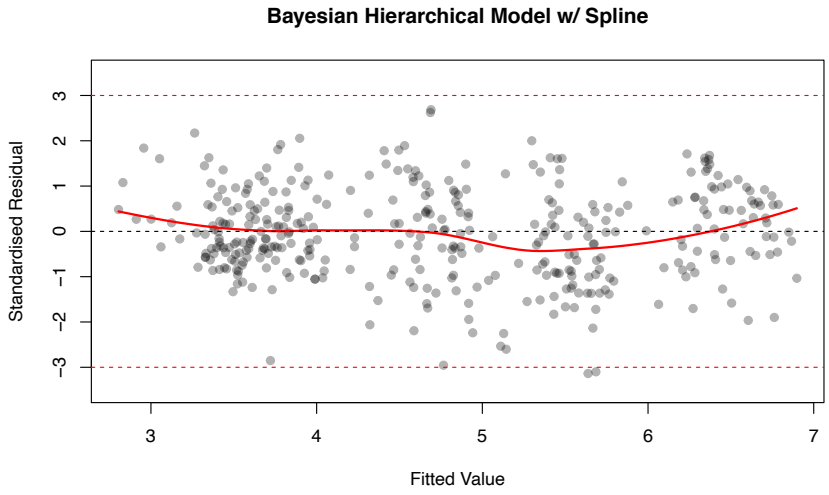
      - where, $K^\tau \equiv (Y - (X(\tau)\beta^{(t+1)} + Z\alpha^{(t+1)}))^T(Y - (X(\tau)\beta^{(t+1)} + Z\alpha^{(t+1)}))$
        Note: $X(\tau)$ is a design matrix with knot τ included. If this step is used, update the notation in the above Gibbs Sampler accordingly.
    - Draw a proposal τ^* from $\tau^*|\tau^{(t)} \sim TruncNorm(\mu = \tau^{(t)}, \sigma^2 = \delta, l = 0, r = \infty)$
    - Calculate $a = \min(1, \frac{p(\tau^*|\cdot)q(\tau^{(t)}|\tau^*)}{p(\tau^{(t)}|\cdot)q(\tau^*|\tau^{(t)})})$
      - where $q(a|b)$ is the density of a truncated normal distribution evaluated at a, with $\mu = b$ and $\sigma^2 = \delta$ as in the proposal density)
    - Draw $U \sim Unif(0,1)$
    - If $U \leq a$, then
      - $\tau^{(t+1)} = \tau^*$
    - Otherwise
      - $\tau^{(t+1)} = \tau^{(t)}$

D Residual Model Diagnostics

Model diagnostics comparing the fitted values against their standardized residuals. We see that the knot that was included corrects the model misspecification for lower fitted values.

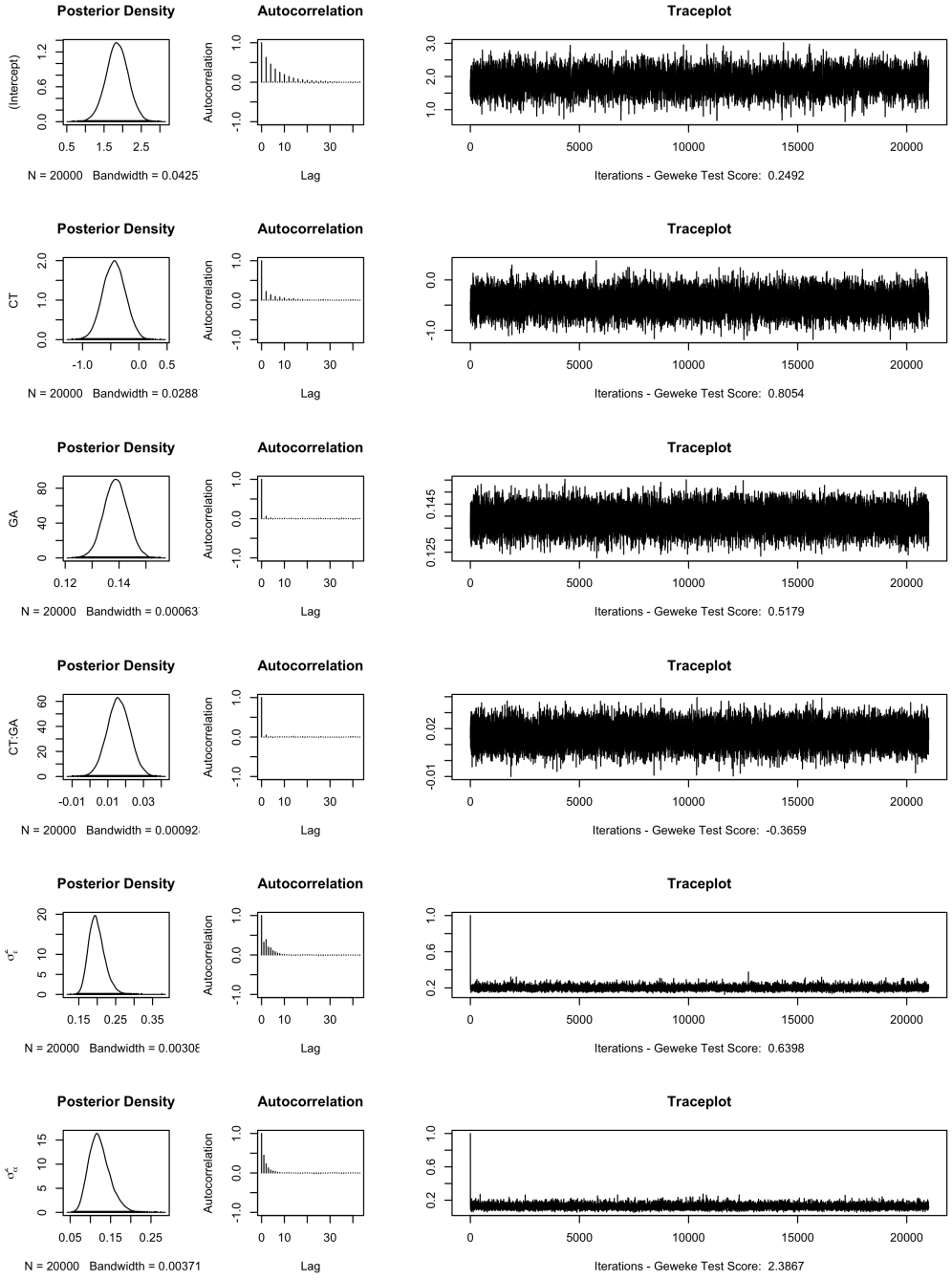






E Bayesian Heirarchical Posterior Sampling Diagnostics

Diagnostics included for the primary variables of interest. All other variables have converged as required and can be submitted if necessary.



F Bayesian Heirarchical (With Spline) Posterior Sampling Diagnostics

Diagnostics included for the primary variables of interest. All other variables have converged as required and can be submitted if necessary.